

VCU Pharmacology & Toxicology

Chairman's corner



Dr. Billy R. Martin

by Dr. Billy R. Martin

I am pleased to report that the Virginia Commonwealth University Department of Pharmacology and Toxicology continues to thrive. The past year has been a very exciting time as we continued to expand our cutting-edge research programs, recruited new faculty and added outstanding candidates to our graduate program.

One of our leading faculty members, Dr. Richard G. Moran, was recently appointed interim director of VCU's Institute for Structural Biology and Drug Discovery. His intimate knowledge of the institute and its capabilities will provide us with new opportunities as we look to the future.

As I reported in the Summer 2006 newsletter, the School of Medicine has undertaken an aggressive campaign to recruit new talent. We have taken maximum advantage of this initiative by recruiting four new faculty members during the past year. We are proud to highlight the careers of these individuals: Drs. Kurt F. Hauser and Nazira El-Hage (both formerly of the University of Kentucky), Dr. Darlene H. Brunzell (formerly of Yale University) and Dr. S. Stevens Negus (formerly of McLean Hospital at Harvard

Medical School). Two additional recruits will join us soon, for a total of six new faculty members.

Our faculty and alumni continue to be recognized for their accomplishments in the areas of scholarship, teaching and service, as you will see in articles about Drs. Robert L. Balster, Edward J.N. Ishac, Leslie S. Satin and William L. Dewey.

We are particularly pleased that Dr. Dale L. Morris was named by the MCV Foundation as the School of Medicine's Outstanding Alumnus in Health Sciences in 2007.

As many of you know, Dr. Louis S. Harris is the visionary who transformed the department into what it is today. We had an opportunity to recognize this accomplishment and his continued dedication to the department in a celebration on his 80th birthday. We owe a great debt of gratitude to Dr. Dewey, who organized this outstanding scientific and social program.

Each year, the department takes part in a retreat that is devoted solely to research. Last year's event was held in Williamsburg, Va., and was attended by more than 100 faculty members, postdoctoral fellows and graduate students. The retreat includes short presentations by faculty to inform others of their current research activities, many informal discussions and poster presentations by trainees. While these activities are very stimulating for all, the graduate students revel in devising after-dinner games that put faculty members in their place.

In December 2007, more fun was had at our annual gala held at the Plant Zero Art Center in Richmond, Va. The gala is always a special time when everyone in the department can share in food, drink, dancing and camaraderie.

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Department benefits from VCU institute

“If you want to understand function, study structure.” This statement has been attributed to Francis Crick, and the rubric contains good advice for scientists young and old. It is common for investigators to study the function of a protein or a macromolecular complex for years and then continue their studies on a higher level after the structure of the protein has been solved.



Drs. Rick Moran, Donald Abraham and Terry Jones

Professor Donald Abraham of the Department of Medicinal Chemistry founded the Institute for Structural Biology and Drug Discovery 10 years ago on the MCV Campus. Dr. Abraham positioned VCU substantially ahead of the field, bringing crystallography to the university at a level that would have been expected only in a much larger university community.

Structural biology at VCU had reached a critical moment and the university viewed the time as both a new opportunity and a crucial decision point. A recent external review of the Institute for Structural Biology and Drug Discovery made a series of recommendations that assisted VCU in developing a path for development. In July 2007, Dr. Richard Moran was appointed interim director of the institute. The investigators that comprise this institute are experienced in X-ray crystallography, high field macromolecular nuclear magnetic resonance, molecular modeling, computational chemistry, protein chemistry and enzymology.

The study of pharmacology at VCU has enormous potential to benefit from the institute and its continued growth. Structural information currently plays a major role in pharmacology and toxicology, contributing fundamental information in two major areas: detailed mechanistic insights and structure-based drug design. When one has an assignment of the three-dimensional coordinates of a protein (which is the initial endpoint of a crystallography project), one can see the orientation of amino acid residues that carry out an enzymatic reaction or form a receptor. The solved structure now allows enormous new insights and opportunities such as site-directed

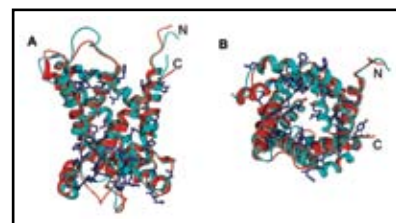
mutagenesis, which has the potential to be the most useful and allows the test of hypotheses related to function and/or mechanism. How does an enzyme reaction work on the bio-organic chemistry level? Why didn't that one member of a closely related series of drugs bind to a receptor? And, perhaps the most important consideration, how do you design a drug that will perfectly fit within the three-dimensional space of an active site or receptor surface?

Another aspect of the activities in the institute of interest to the Department of Pharmacology and Toxicology has been the development of a course in molecular modeling taught by Drs. Glen Kellogg and Richard Westkaemper of the Department of Medicinal Chemistry. This course serves as an entry point for our students into molecular modeling and the interface of modeling with analysis of the hundreds of structural coordinate sets deposited in the protein data base (PDB).

An example of the benefit of this course is drawn from the dissertation research of Scott Lawrence, a doctoral student in the Moran laboratory. Lawrence's research focuses on understanding the process whereby folate compounds enter the mitochondria and the effect of chemotherapeutic antifolates on this transport process. He came to this study armed with a newly isolated inner mitochondrial membrane transporter that facilitates entry of folates into the mitochondrial matrix and a recent solution of the structure of a member of this protein family, entered into the PDB by Gerard Brandolin and his colleagues in Grenoble, France. Since the X-ray crystal structure of this prototype inner membrane carrier, the ADP/ATP exchanger, had enough homology to the folate carrier and was of high resolution, Lawrence was able to construct a homology model that threaded

the folate carrier through the known structure of the ADP/ATP carrier. This gave a working model of the folate carrier and has allowed a series of site-directed mutagenesis experiments to be designed that have clarified the mechanism of ligand transport through the membrane.

The advantages offered by structural biology bring a new dimension to our faculty and students in the Department of Pharmacology and Toxicology from both a research and an educational perspective.



Homology model for the hamster mitochondrial folate transporter (blue-gray) superimposed on the crystal structure of the bovine ADP/ATP exchange (red). In figure A, the structures are oriented so that the inner mitochondrial membrane would be perpendicular to the plane of the page. In figure B, the structure in figure A has been rotated 90 degrees, so that the view is from the intermembrane space down into the transport cavity.

Balster presented with two prestigious awards

In December 2006, the American Psychological Association presented Robert L. Balster, Ph.D., with a Distinguished Service to Psychological Science Award for his extraordinary service to the psychological sciences. His service to psychology and psychopharmacology throughout his academic career has been broad and significant. Dr. Balster has held key leadership positions in professional psychological and psychopharmacological organizations, including the American Psychological Association. He has served on numerous governmental advisory panels and grant review committees, and serves as editor and on editorial boards of several psychopharmacological journals. Dr. Balster also has served the field through his teaching and mentoring of students, many of whom have gone on to become national leaders in the field. These and other service activities to the psychological sciences, his kind demeanor and his ability to listen to others have gained him the widespread respect and appreciation he so richly deserves.

On Aug. 17, 2007, at the annual convention of the APA in San Francisco, Dr. Balster received the Brady-Schuster

Award from the APA Division of Psychopharmacology and Substance Abuse. The award honors a scientist who “conducts outstanding research underscoring the fundamental importance of behavioral science to psychopharmacology or substance abuse.” The award is named for two of the early leaders in behavioral pharmacology research, Drs. Joseph V. Brady and Charles R. Schuster.



Dr. Robert L. Balster

Dr. Balster is currently the Luther A. Butler Professor of Pharmacology and Toxicology and director of the Institute for Drug and Alcohol Studies at Virginia Commonwealth University. His research focuses on neurobehavioral pharmacology and substance abuse.

Harris Research Symposium held at VCU



Dr. Louis S. Harris

On May 16, 2007 the Department of Pharmacology and Toxicology celebrated the 80th birthday of its former chairman, Dr. Louis S. Harris. Participants in the two-day symposium held at Virginia Commonwealth University included 12 of the world's leading drug abuse researchers. The symposium highlighted the major contributions of the field during the past half-century and some of the most interesting cutting-edge research going on today.

The department faculty and guests honored Dr. and Mrs. Harris at a memorable dinner that featured congratulatory remarks by university officials and many outstanding scientists from around the world. A wonderful slide show depicting Dr. Harris' life was shown on monitors throughout breaks, the reception and dinner. (Visit the department alumni Web site to view pictures.)

In 1972, Dr. Harris assumed the role of chair of the department and guided its rapid and extensive expansion over the next 20 years.

The graduate program, the externally funded research and the department's national stature all significantly increased throughout his tenure. Dr. Harris continues to contribute to the department and the larger university community in many ways and maintains a productive, federally-funded research program. Dr. Harris and his wife, Ruth, have established a number of professorships and have donated to many programs throughout the university.



Dr. Harris and wife Ruth with department members and honored guests

Faculty honored for teaching excellence

The School of Medicine's highest honor, the Faculty Excellence Award, is given annually to a faculty member who is an outstanding teacher and has a compelling record of contributions to medical education. As an educator, the individual is widely recognized for educational leadership and academic inquiry. The faculty member supports the educational excellence of colleagues and embodies a spirit of instructional innovation. The Department of Pharmacology and Toxicology is honored to have had faculty members receive this prestigious award for the past two years.

Dr. Edward J.N. Ishac

Dr. Edward J.N. Ishac, associate professor in the Department of Pharmacology and Toxicology, received the School of Medicine's Faculty Teaching Excellence Award in 2006.

"What makes Eddy really a cut above all the other talented teachers at VCU is his ability to employ his considerable talent with computers and computer systems toward making his teaching even more effective," said George Kunos, M.D., Ph.D., scientific director, NIAAA/NIH.

"To complement and enhance course material, Dr. Ishac has created multiple Web sites for various courses offering a plethora of links, audio PowerPoint presentations, video clips to illustrate many topics and online quizzes," wrote Stephen T. Sawyer, Ph.D., the department's professor and vice chair for education.

In the words of one M-II student, "Dr. Ishac's Web site rocks!"



Dr. Edward J.N. Ishac

"Dr. Ishac's contributions as a medical educator extend far beyond technology. He is the most dedicated and truly outstanding educator that I have met in my almost 40 years in medical schools," praised William L. Dewey, Ph.D., professor in the Department of Pharmacology and Toxicology. "His contributions include outstanding and well-received formal lectures to students in class, excellence as course director, unending availability to students outside of

class, immense commitment and outstanding use of new technological methods to foster self-learning and improving the excellence of teaching of the faculty. He clearly loves to teach. He is, in fact, always teaching."

"Dr. Ishac has a passion for teaching that goes far beyond that of a typical faculty educator. He manages to build a strong bond with every class he teaches," agreed Billy R. Martin, Ph.D., Harris Professor and chair of the Department of Pharmacology

and Toxicology. As evidence, Dr. Ishac has been selected as professor of the year in the department numerous times and has been named the School of Medicine outstanding teacher every year in which he has taught in M-II medical pharmacology.

Dr. Leslie S. Satin

In 2007, Dr. Leslie S. Satin, professor in the Department of Pharmacology and Toxicology, received the School of Medicine's Faculty Teaching Excellence Award. Colleagues praise Dr. Satin's genuine passion for teaching.



Dr. Leslie S. Satin

"He has the ability to engage the students and impart critical skills needed for biomedical research," said Billy R. Martin, Ph.D., chair of the Department of Pharmacology and Toxicology.

There is something about the way Dr. Satin approaches teaching that makes him stand out, both to his students and his colleagues. Perhaps the raves he receives are all the more remarkable given his subject matter, which is anything but easily digestible.

"Dr. Satin teaches rather complex topics related to neuromuscular junction pharmacology, anti-arrhythmics and calcium channel blockers," explained Laura Sim-Selley, Ph.D., associate professor in the Department of Pharmacology and Toxicology. "He is aware that education is more than grades and is sincerely dedicated to furthering the knowledge of students."

"It is one thing to contribute to the educational mission of a single department, quite another to influence a discipline at the school level," writes William L. Dewey, Ph.D., professor in the Department of Pharmacology and Toxicology. "Using his interdisciplinary background, Les has been able to exert leadership in the cellular neuropharmacology area and by doing so has created several courses, most notably the neuroscience graduate-level course that started in 1992 and blossomed. ... The course has evolved into "Cellular Molecular Neuroscience" and become the focal point for our developing neuroscience curriculum and the neurosciences doctoral program. Les led the effort to get the neuroscience doctoral program approved by SCHEV and that will undoubtedly increase its ability to recruit and train neuroscience students."

In addition to classroom teaching, Dr. Satin has trained doctoral and postdoctoral students and has found time to assist undergraduate and high school students as well.

A VCU affiliate expands its influence

The numbers couldn't be clearer: More than 50 million Americans live with some sort of disability. The Partnership for People with Disabilities, an affiliate of VCU's School of Education, which is directed by Dr. Fred Orelove, is the state's only university center for excellence in developmental disabilities and is funded by the Federal Administration on Developmental Disabilities. Alumni and faculty from the schools of Education, Medicine, Social Work, Nursing, Allied Health Professionals and other VCU schools have helped the partnership achieve its mission of helping people with disabilities become full members of their communities.

William L. Dewey, Ph.D., professor in the Department of Pharmacology and Toxicology, joined the partnership's Consumer Advisory Council 18 years ago. He quickly became the partnership's chairperson, a volunteer commitment he's held ever since.

"I wouldn't have spent 18 years as chair of the advisory board if I didn't really believe in what the partnership does," Dr. Dewey said.

Dr. Dewey credits the partnership for researching new and better ways to teach educators about people with disabilities. Going forward, he sees a role for the partnership in educating more health care providers in disability awareness issues.

"People with disabilities have the same health problems as everyone else," Dr. Dewey said. "Medical professionals must learn to deal sensitively with the needs of people with disabilities because we all have disabilities. Some are just more obvious than others."

Dr. Dewey speaks not only as a scientific colleague. As the parent of a disabled child, he appreciates the information and support that the partnership provides. Dr. Dewey's daughter, Reenie, age 42, has a vocabulary of perhaps 25 words. Dr. Dewey still remembers how hard it was to find a dentist to treat Reenie when the family first moved to Virginia 30 years ago. "It was so sad," he said. "People wanted to put folks like Reenie aside and ignore them."



Drs. Fred Orelove and William L. Dewey

An interdisciplinary center, the partnership supports people with disabilities by conducting research and evaluation initiatives, training and providing technical assistance, disseminating information, and influencing public policy. For infants, the partnership trains early interventionists and early childhood educators in the newest techniques and approaches to inclusion and maintains family peer networks.

Activities on behalf of school-age children range from leadership training for professionals over a broad range of disciplines to enhancing school nurses' effectiveness in working with children with disabilities. For adults, the partnership is devising innovative strategies using assistive technology to help people with disabilities direct their own lives.

When the partnership was founded in 1985, it boasted a professional staff of five. Today more than 80 health and education professionals manage more than 24 funded projects. Many MCV Campus alumni, faculty and supporters have helped the partnership grow to its current stature. Their motivations for supporting the partnership are as varied as the issues the partnership addresses.

Within the community, MCV Campus alumni are employed as school nurses, occupational and physical therapists, psychologists and social workers. They are supervisors and mentors to the next generation of trainees being prepared to support individuals with disabilities. Those trainees in turn become professionals with heightened sensitivity to the needs of families who have a member with a disability — and thus more effective in their jobs.

"More importantly, people with developmental disabilities, many of whom have been hidden from view, will receive high quality, coordinated health care and other supports needed to live with dignity and greater independence," Dr. Dewey said.



Bill, Reenie and Pat Dewey

Focus on alumni: Dale L. Morris, Ph.D.

Class of 1991

In 1991, Dr. Dale L. Morris received his doctorate specializing in immunotoxicology under the direction of Dr. Michael Holsapple. Dr. Morris then joined the laboratory of Dr. Thomas Rothstein at Boston University Medical Center as a postdoctoral fellow, investigating the signal transduction pathways and transcriptional regulation of early growth response genes during B lymphocyte activation and its relationship to the onset of autoimmune disorders and B lymphocytic leukemias.

In 1993, Dr. Morris was recruited by G.D. Searle and Co. in Skokie, Ill., to help address regulatory agency concerns about the potential immunomodulatory effects of anti-inflammatory and HIV therapies.



Dr. Dale L. Morris

At the same time, investigative or experimental toxicology was an evolving paradigm within the industry, with particular emphasis on molecular biology and biochemical approaches to investigate the mechanisms of drug-induced toxicity. With a background in experimental pharmacology, toxicology, immunology, biochemistry and molecular biology, Dr. Morris was given the opportunity to build and lead an experimental toxicology group at Searle, whose mission was to support drug discovery and research, as well as to investigate the mechanisms of organ toxicities observed in preclinical toxicology studies conducted in support of compound development. This group investigated toxicities ranging from liver and pancreas toxicity to bone marrow and immunotoxicity, and was highly successful in helping to advance a number of key programs and compounds to clinical use.

With the success of the experimental toxicology group in Illinois, Dr. Morris was asked to relocate to the Monsanto World Headquarters in St. Louis in 1997 to begin building an experimental toxicology and pathology group to support a much larger — and expanding — drug discovery and research organization at that site. This provided the opportunity to integrate toxicology

into the experimental design and allowed drug candidates in late-stage development for arthritis to incorporate improved safety attributes to reduce the potential for adverse drug effects.

Following Monsanto's merger with Pharmacia and Upjohn in 2000, Dr. Morris accepted a two-year assignment within the newly formed Pharmacia Corp. as the site leader for global drug metabolism in Nerviano, Italy, where he helped build an integrated investigative toxicology and drug metabolism group that provided mechanistic toxicology and metabolism support to development programs and discovery research in oncology.

In 2003, Pharmacia was acquired by Pfizer Inc. and Dr. Morris returned to St. Louis, where he is currently the drug safety site lead for research and development. The group is composed of approximately 65 colleagues with expertise in general toxicology, safety pharmacology, anatomic and experimental pathology and investigative toxicology. The therapeutic focus areas for Pfizer in St. Louis include inflammatory diseases, osteoarthritis, rheumatoid arthritis, hepatitis and anemia. The group supports both drug discovery and full development of therapeutic candidates discovered in projects across these research areas.

For students interested in experimental toxicology and drug discovery, Dr. Morris' advice is to look for opportunities to diversify one's skills as much as possible. Throughout his career, he has had the opportunity to apply all the knowledge and tools he has gained in his graduate and postdoctoral training. Experience in experimental pharmacology, biochemical and cellular toxicology, pharmacokinetics, and absorption, distribution, metabolism and excretion (ADME) are essential, as is a good working knowledge of histology, histopathology and experimental pathology techniques. In the field, one encounters chemical and pharmacological-mediated adverse effects of compounds with tremendous diversity in terms of target organs and mechanisms. Even after 13 years in the pharmaceutical industry, Dr. Morris' team is still discovering new and unique target organ toxicities that have never been observed or described. It is the team's job to identify these development-limiting toxicities in the chemical series early in the drug discovery process, fully characterize the toxicity using experimental methodologies, develop *in vitro* models and screening approaches to determine structure-toxicity relationships and eliminate these liabilities through iterations in drug design. The ultimate goal for Dr. Morris and his team is to facilitate the discovery of drug candidates with optimized safety attributes that could some day become safe and effective pharmacotherapies for patients with inflammatory diseases.

In 2007, the MCV Foundation named Dr. Morris the School of Medicine's Outstanding Alumnus in Health Sciences.

Focus on research: S. Stevens Negus, Ph.D.

Behavioral pharmacology of opioids

Dr. S. Stevens Negus, who joined Virginia Commonwealth University in October 2007, earned a bachelor's degree in English from the University of Virginia. He then spent four years as a journalist in the U.S. Army before earning his doctorate in neurobiology in 1990 from the University of North Carolina at Chapel Hill, where he conducted his thesis research in the laboratory of Dr. Linda Dykstra.

From 1990-91, Dr. Negus completed a dual postdoctoral fellowship with Dr. George Koob in the Department of Neuropharmacology at the Scripps Research Institute and with Dr. Matthew Weinger in the Department of Anesthesiology at the University of California at San Diego. He then moved on to a research faculty position in the laboratory of Dr. Jim Woods in the Department of Pharmacology at the University of Michigan from 1991-93. In 1993, Dr. Negus took a position as an assistant profes-

sor in the Department of Psychiatry at Harvard Medical School and he was named director of the neurobiology program in the McLean Hospital Alcohol and Drug Abuse Research Center.

Dr. Negus' research has focused on the behavioral pharmacology of opioids ever since the day as a graduate student he collected his first morphine dose-effect curve in squirrel monkeys behaving in an assay of antinocicep-

tion. Morphine-like opioids, which act at the mu-subtype of the opioid receptor, are effective analgesics. However, their clinical utility is limited by undesirable effects such as tolerance and abuse liability.

Dr. Negus became interested in the investigation of novel opioids that might produce clinically useful effects without undesirable actions. A major finding from this research has been that delta opioid agonists produce analgesic effects in a novel model of inflammatory pain in nonhuman primates and they also enhance the analgesic effects of morphine-like opioids. The abuse liability and other undesirable effects of delta agonists appear to be

minimal, and delta agonists also appear to attenuate some undesirable effects of mu agonists. A major implication of this work is that delta agonists may be useful either alone or in combination with morphine-like analgesics for the treatment of pain. This research has also led to several parallel research projects. First, these studies required the refinement and implementation of data analytic methods for evaluation of drug combinations, and these methods are now being applied to study other types of drug interactions. Second, these studies encouraged development of new behavioral procedures for the preclinical evaluation of (a) pain and analgesia using operant approaches and (b) the reinforcing effects of drugs using choice procedures. Finally, this work on the behavioral effects of opioid drugs has served as a foundation for ongoing pilot studies on opioid-induced brain activation as measured by functional magnetic resonance imaging.

Paralleling this work with opioids, Dr. Negus also has studied the behavioral pharmacology of central nervous system stimulants such as cocaine. The abuse of stimulants alone or in combination with opioids remains a major public health problem and Dr. Negus' research in this area has focused on the identification and evaluation of pharmacological strategies that could reduce the abuse-related effects of stimulants. A major finding of this research effort has been that monoamine releasers with modest selectivity for dopamine versus serotonin release are especially effective in selectively reducing the self-administration of cocaine. Formulations of these compounds may ultimately be useful in the treatment of stimulant dependence in much the same way that methadone is useful for the treatment of opioid dependence.

In addition to his research activities, Dr. Negus has taught and mentored extensively. As a teacher, he has directed several undergraduate pharmacology courses as well as more advanced courses taught to postdoctoral fellows supported by a training grant at McLean Hospital. He has mentored nine postdoctoral fellows, most of whom have gone on to successful careers in academia or industry.

In the area of service, Dr. Negus has contributed to local, national and international entities. He served for 14 years on the McLean Hospital Institutional Animal Care and Use Committee, chairing the committee for 13 years. Dr. Negus has served as a standing and ad hoc member on various NIDA and NIH study sections, and is currently on the editorial board of four pharmacology journals. He also has played an active role in various professional societies, principally the College on Problems of Drug Dependence. Dr. Negus just completed a four-year term on the CPDD Board of Directors and, as chair of CPDD's Committee on Abuse Liability Testing, he organized a conference that drew more than 70 participants from 11 countries in Europe, North America and Asia.



Dr. S. Stevens Negus

Focus on research: Kurt F. Hauser, Ph.D.

Opioid-mediated central nervous system plasticity and the pathogenesis of HIV-1

Dr. Kurt F. Hauser received his undergraduate degree in psychology with minors in chemistry and fine arts from Rutgers, The State University of New Jersey, in 1977. In 1983, he earned a doctorate in anatomy, studying neuroscience at the University of Medicine and Dentistry of New Jersey. Dr. Hauser then moved to the laboratory of Dr. Dominique Toran-Allerand at Columbia University where he studied neuroscience and the effects of steroid hormones and neuropeptides on central nervous system plasticity from 1983-86.

After joining the Pennsylvania State University Medical Center as an instructor from 1986-87, Dr. Hauser was recruited to the University of Kentucky Department of Anatomy and Neurobiology as an assistant professor. He was promoted to associate professor with tenure in 1992, and was subsequently promoted to professor in 2000. Dr. Hauser taught "Medical Histology" from 1987-2006 and served as course director from 1996-2000. He has also taught in the graduate cell biology, cell and molecular development, behavioral science and pharmacy programs while at the University of Kentucky.

In July 2007, Dr. Hauser joined the faculty of Virginia Commonwealth University, where he is currently a professor in the Department of Pharmacology and Toxicology and member of the Institute for Drug and Alcohol Studies.

Dr. Hauser has established an international reputation in the field of opioid drug abuse and CNS plasticity. He has been a visiting faculty member at the Center for Molecular Medicine, the Karolinska Institute, the University of Innsbruck in Austria, the Technical University of Munich in Germany, the Federation of European Neuroscience Societies and the International Brain Research Organization.

Dr. Hauser was an international organizer of the European Neurochemistry Winter Conference from 1999-2003, and also serves on the council of the Society for NeuroImmune Pharmacology. His laboratory has been funded by the NIH continuously since 1990 and he currently holds two NIH grants including a Program Project grant. Additionally, Dr. Hauser has been a regular member of the NIH study sessions for Molecular, Cellular and Developmental Neuroscience from 1998-2002, and NeuroAIDS and other End-organ Diseases from 2003-07. He continues to review grants ad hoc for both federal and private foundations.

Dr. Hauser's research has historically been directed toward understanding the mechanisms by which opioids regulate

neuroplasticity in the CNS. In recent years, he has focused upon how opioid exposure increases CNS vulnerability to neuroAIDS. Up to 90 percent of those infected by the human immunodeficiency virus will have CNS involvement. This may include a subclinical CNS HIV infection, subtle motor cognitive deficits or a progressive, severe dementia.

Early in his career, Dr. Hauser found that endogenous opioids could modify dendritic plasticity and synaptic organization during maturation. Based on these initial findings and work in other laboratories that showed that high levels of opiate drugs can cause alterations in neural development, his laboratory described how endogenous opioids and opiate drugs could regulate the maturation of subpopulations of opioid receptor expressing neurons, astrocytes and oligodendrocytes. Dr. Hauser's laboratory also was instrumental in showing that developing cells can express opioids that act through autocrine/paracrine mechanisms to regulate maturation. More recently, the laboratory's efforts have focused on understanding drug actions related to HIV-induced CNS pathology.

Studies by Dr. Hauser's laboratory also have found that opioid drugs can intrinsically exacerbate the inflammatory and neurotoxic effects of HIV-1 in the CNS, and that neuronal injury and inflammation can occur through direct actions on the opioid receptors that are expressed on neurons and astroglia. The opioid system thus appears to play a fundamental role in the pathogenesis of AIDS. The progression to AIDS, especially neuroAIDS, in HIV-seropositive individuals may be markedly altered in opiate drug abusers as compared to non-abusers. Although the virus itself propagates in microglia and astroglia, HIV-1 proteins such as gp120 and Tat are subsequently released and cause functional and degenerative changes in neighboring neurons and astroglia.

Current efforts are aimed at better defining the mechanisms of convergent signaling whereby heroin drug abuse exacerbates HIV encephalitis and/or AIDS-associated dementia through coordinated direct actions on astroglia, microglia and neurons.



Dr. Kurt F. Hauser

Focus on research: Nazira El-Hage, Ph.D.

Glial regulatory pathways in opiate abuse and HIV neuropathogenesis

In July 2007, Dr. Nazira El-Hage joined the Virginia Commonwealth University Department of Pharmacology and Toxicology as an assistant professor. She completed a bachelor's degree in biological sciences, a master's degree in mycology and a doctorate in microbiology, immunology and molecular genetics all from the University of Kentucky. Dr. El-Hage's graduate work



Dr. Nazira El-Hage

focused on surface proteins of the spirochete *Borrelia burgdorferi*, which is the infectious agent in Lyme disease, and characterized the interactions of these pathogenic proteins with vertebrate tissues.

Dr. El-Hage pursued a postdoctoral scholarship in the Department of Virology at the University of Kentucky with Dr. George Luo. Research focused on the nonstructural viral proteins of the hepatitis C virus: the sites

where HCV RNA is replicated and the virus components of the HCV replication complex. In May 2003, she joined the laboratory of Dr. Kurt Hauser as a senior scientist to explore opioid drug and human immunodeficiency virus-type 1 toxic interactions in the central nervous system.

Dr. El-Hage's current research program focuses on three areas that include an examination of the sites of convergence where opioids exacerbate inflammatory cytokine expression in astrocytes through the activation of NF- κ B; determining the extent that the release of inflammatory chemokines cause neuronal damage and gliosis; and elucidating the role of Toll-like receptors in mediating opioid drug-HIV-1-induced inflammation, reactive gliosis and neuronal injury in the CNS.

It is estimated that 15 percent to 40 percent of AIDS patients have significant neurological complications, and substance abuse dramatically increases the spread and the severity of the CNS complications of HIV-1 infection. Dr. El-Hage's work has shown that HIV virotoxins such as gp120 and Tat are likely to be neurotoxic through direct actions on glia. Moreover, her work has found that opiates acting at mu-opioid receptors (MOR) synergistically enhance HIV-1 neurotoxicity in a large part by directly stimulating the release of inflammatory chemokines by MOR-expressing subpopulations of astrocytes. Understanding the involvement of astrocytes in shaping the immune response will likely provide new insights into the intrinsic response of the CNS to pathogenic insults and better interventions for treating substance abuse and neuroAIDS.

Focus on research: Darlene H. Brunzell, Ph.D.

Neuropharmacology of drugs of abuse and mental illness

Dr. Darlene H. Brunzell graduated with a bachelor's degree in psychology and communications from the University of Wisconsin-Eau Claire in 1992. Her newly found interest in brain function led Dr. Brunzell to pursue a doctorate in neuroscience and behavior at the University of Massachusetts. As a graduate student, she worked with Dr. John W. Moore, studying computational and animal behavioral models of learning and memory, and continued her training with Dr. Jerrold S. Meyer. Dr. Brunzell received her doctorate in 1999, and was honored with a New Investigator Research Award from the Neurobehavioral Teratology Society for these studies in 2002.

Dr. Brunzell pursued postdoctoral training at Yale University, first in the Department of Psychology with Dr. Jeansok Kim, where she studied the neuroanatomical basis of fear learning, and then with Dr.

Marina R. Picciotto, where she expanded her scientific repertoire to include behavioral genetics and molecular biology. In 2005 Dr. Brunzell was promoted to faculty in the division of molecular psychiatry at the level of associate research scientist. Her studies were among the first in mice to explore the effects of *in vivo* nicotine exposure on second messenger signaling. Dr. Brunzell showed that chronic



Dr. Darlene H. Brunzell

See Brunzell, continued on Page 10

Brunzell continued from Page 9

nicotine exposure alters ERK and CREB signaling in areas of the brain that contribute to addiction, learning and mood. She also discovered that the beta 2 subunit of the nicotinic acetylcholine receptor is critically involved in nicotine-associated enhancement of cue rewards. In 2005, the Society for Research on Nicotine and Tobacco recognized Dr. Brunzell with a Jarvik-Russell Young Investigator Award for her contributions to the field of nicotine and tobacco research.

Dr. Brunzell has served as reviewer for prestigious journals in the field of neuroscience and drug abuse research, is an associate editor for *Nicotine and Tobacco Research*, the official journal of the Society for Research on Nicotine and Tobacco, and has participated in the grant review process for the state of Florida as well as for the Canadian Tobacco Control Research Initiative, where she served as committee chair in 2007.

Dr. Brunzell has won a Young Investigator Award from the National Alliance for Schizophrenia and Depression Research, pilot project support from the Center for Nicotine and Tobacco Use Research at Yale and is currently funded by NIDA to explore the contributions of distinct nicotinic receptor subunits to the primary rewarding effects of nicotine versus nicotinic receptor regulation of cue learning and motivation.

Dr. Brunzell joined the Virginia Commonwealth University Department of Pharmacology and Toxicology as an assistant professor in September 2007. Combining molecular, neurochemical and behavioral techniques, her goal is to understand how single molecules contribute to complex behaviors that support drug addiction and mental illness phenotype. The ultimate goal of Dr. Brunzell's research in rodents is to identify more effective pharmacological and behavioral interventions for drug addiction, anxiety and schizophrenia in humans.

Remembering our colleague, our friend

Edward R. Bowman, Ph.D.



Dr. Edward R. Bowman

Dr. Edward R. Bowman, research associate in the Department of Pharmacology and Toxicology, passed away on Jan. 26, 2008. He is survived by his wife of 53 years, Wilma; his daughter, Gay Bowman; brothers, William Bowman, Lance Bowman and Garland Bowman; and sisters, Elizabeth Woody, Barbara Fogus and Mary Shrader.

Dr. Bowman was a U.S. Army veteran and served in World War II and the Korean War. After earning his bachelor's degree in biology and chemistry at Concord College, he completed a master's degree in physiology at West Virginia University. In the spring of 1956, he came to Virginia Commonwealth University as a research assistant in our department and completed his doctoral degree in pharmacology in 1963. Since then, he has served on the department faculty as a research associate.

In his career, Dr. Bowman dedicated a quarter-century to the study of the metabolism of nicotine in several mammalian species, including humans. An especially notable contribution was his discovery of a simple, elegant and direct method for the synthesis of stereoisomers of nicotine. As pioneers in this field, he and his co-workers were the first to identify at least 10 metabolites of nicotine without the aid of some of the more modern instrumentation available today.

Since 1985, on behalf of the National Institute on Drug Abuse and the College on Problems of Drug Dependence, Dr. Bowman was

involved in the evaluation of more than 500 compounds for their abuse liability. He participated in preclinical studies in nonhuman primates on the duration of action and efficacy of depot preparations of naltrexone and buprenorphine. Comparable preparations are now used in the therapy of human opioid abuse.

As his research progressed, Dr. Bowman authored or co-authored some 160 articles on his findings in some of the scientific field's leading publications. He belonged to several professional societies, including the American Chemical Society, the American Society of Pharmacology and Experimental Therapeutics and the Society for Experimental Biology and Medicine. In addition to his research interests, Dr. Bowman also taught in the schools of Pharmacy, Dentistry and Medicine. Ed, as he was known, was an unassuming and witty man. Above all, he was a gentleman. He will be missed.



Dr. Edward R. Bowman and family

Graduate corner: student and alumni news

Doctoral students gain NIH support

Many NIH institutes provide National Research Service Awards to support doctoral-level training. These institutes award NRSA individual predoctoral fellowships to promising applicants with the potential to become productive, independent investigators in the scientific mission areas of these institutes. We are honored to have four predoctoral students currently supported by NRSAs.

Jennifer Wolstenholme; advisor, Dr. Mike Miles “Behavioral and molecular analysis of individual variation of ethanol drinking”

The Miles laboratory has observed a robust and persistent individual variation in ethanol drinking within an inbred mouse strain. Wolstenholme’s research will characterize the behavioral and molecular profiles of individual mice within a strain (which reduces the variability due to genetic factors) to study the effect of social defeat on the modulation of ethanol drinking. She says that “we expect that these experiments will aid in the understanding of the environmental influences contributing to these individual differences in ethanol drinking.”

Phil Yeager; advisor, Dr. Les Satin “Traumatic brain injury (TBI) effects on neuronal GABA currents”

The Satin laboratory has been evaluating the pharmacological properties of GABAA receptors using whole cell patch clamp technique in neuronal cultures. Yeager is determining if stretch-injury alters the functional properties of GABAA receptors by applying drugs and measuring whole cell currents under voltage clamp conditions. He expects these experiments to aid in the evaluation of the cellular and molecular mechanisms that cause TBI, and may uncover novel therapies to treat brain-injured patients, who suffer greatly from cognitive as well as motor impairments.

Christopher Sheth; advisor, Dr. Kimber White “Tolerance to the immunosuppressive effects of delta-9-tetrahydrocannabinol (THC)”

Sheth’s research is focused on the development of tolerance to cannabinoid-induced suppression of the immune system. He proposes to identify the specific immune cell type(s) responsible for

THC-induced suppression of humoral immunity, as measured via the IgM antibody forming cell assay, and the particular mechanism(s) by which this occurs.

Alexander Putnam; advisor, Dr. Mike Miles “Genetic and genomic analysis of ethanol anxiolysis”

Utilizing an approach combining behavioral genetics and expression profiling, ethanol-induced anxiolysis-like behavioral quantitative trait loci (QTL) were identified and superimposed with brain microarray data to correlate ethanol-responsive gene expression patterns with behavioral QTL data, thereby identifying genes influencing variation in the ethanol-induced anxiolysis phenotype.

Student awards

Students receiving awards in the department include: Denise Hernandez, recipient of the 2006 Lauren A. Woods Award and the 2007 MCV Foundation Health Sciences Graduate award, advisor Dr. Kimber White; and Scott Lawrence, recipient of the 2007 Anthony Ambrose Award, advisor, Dr. Rick Moran.

Latest graduates

Congratulations to our most recent graduates: Denise Hernandez, (Ph.D., advisor Dr. Kimber White), Vanessa Peachee (Ph.D., advisor Dr. Kimber White), Brittany Carlson (M.S., advisor Dr. Aron Lichtman), Lisa Merritt (M.S., advisor Dr. Imad Damaj) and Andrew Meng (M.S., advisor Dr. Tai Liang Guo).

PTSO

Current officers in the Pharmacology and Toxicology Student Organization are Scott Lawrence, president; Aditi Martin, vice president; Sean Farris, secretary; Lamont Booker, treasurer; Brendan McCay and Jerry Wright, SGA representatives; Chris Sheth and Uzo Mba, honor council representatives; Scott Rothbart, recruitment; and Kia Jackson, library representative. If you have any questions regarding PTSO, please contact Lamont Booker at bookerl@vcu.edu.

Request for news items

Have you changed employment, been promoted or received an award or honor recently? Share your good news. Please forward your information to eishac@vcu.edu. Remember, this is your newsletter and your contributions or suggestions are appreciated.

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Contributions

We welcome your contributions. Please send any news and information to:

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